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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FORD, VANESSA L	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 04/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/786,435	KRIEGLSTEIN, KERSTIN	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-8 and 11-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-8 and 11-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *3/3/05*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

FINAL ACTION

1. Applicant's amendment and response filed December 3, 2004 is acknowledged. Claims 1, 5 and 14-15 and 17 have been amended. Claims 2-4 and 9-10 have been cancelled.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

Rejection Withdrawn

3. In view of Applicant's amendment and response the following objections or rejections are withdrawn:

a) Rejection of claims 1 and 14-18 under 35 U.S.C. 112, second paragraph , page 5, paragraph 5 of the previous Office action.

b) Rejection of claims 5-8 and 11-13 under 35 U.S.C. 112, second paragraph , page 5, paragraph 6 of the previous Office action.

c) Rejection of claim 14 under 35 U.S.C. 112, second paragraph , page 5, paragraph 7 of the previous Office action.

New Grounds Necessitated by Amendment

Claim Objections

4. Claim 6 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 11. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. Claim 12 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 13. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 5-8 and 11-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.*

The claims are drawn to a method for inhibiting the biological activity of transforming growth factor β on damaged neurons in cerebral disorders, said method comprising the steps of providing a patient having damaged neurons said damaged neurons resulting from a cerebral disorder wherein said cerebral disorder is not intentionally induced and treating said damaged neuron in said patient with a compound that inhibits the biological activity of TGFβ on damaged neurons. The amended claims contain new matter. Applicant has amended the claimed invention from a method of inhibiting the biological activity of TGFβ providing a patient having damage neurons resulting from a cerebral disorder to a method of inhibiting the biological activity of TGFβ providing a patient having damage neurons resulting from a cerebral disorder wherein said cerebral disorder is not intentionally induced. Applicant has not set forth where in the instant specification that support can be found for the amended claims.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1, 14-15 and 18 are rejected under 35 U.S.C. 102(b) as anticipated by Logan et al *(MEETING ON FGF, ENDOTHELIAL CELL GROWTH FACTORS AND ANGIOGENESIS HELD AT THE 20TH ANNUAL MEETING OF THE KEYSTONE SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 1-7, 1991. J CELL BIOCHEM SUPPL).*

Claims 1, 14-15 and 18 are drawn to a method for inhibiting the biological activity of transforming growth factor β on damaged neurons in cerebral disorders said method comprising the steps of providing a patient having damaged neurons, said damaged neurons resulting from a cerebral disorder, wherein said cerebral disorder is not intentionally induced; and treating said damaged neurons in said patient with a compound that inhibits the biological activity of TGF-β on said damaged neurons.

Logan et al, 1991 teach a method of inhibiting biological activity (scar formation) on mammals that had central nervous system injuries (i.e. not intentionally induced) by infusing the mammals with TGF-β blocking antibodies. Logan et al teach that these mammals showed reduced fibrotic scar of limited depth (see the Abstract).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Claim Rejection - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1, 5-8 and 11-18 are rejected under 35 U.S.C. 103(a) as unpatentable over Logan et al *(MEETING ON FGF, ENDOTHELIAL CELL GROWTH FACTORS AND ANGIOGENESIS HELD AT THE 20TH ANNUAL MEETING OF THE KEYSTONE SYMPOSIA ON MOLECULAR AND CELLULAR BIOLOGY, KEYSTONE, COLORADO, USA, APRIL 1-7, 1991. J CELL BIOCHEM SUPPL)* in view of Logan et al *(Brain Research, 587, 1992, p. 216-225)* and in further view of Alexander et al *(Neurosurgery, 1990, 26/4, p. 559-564, (Abstract only))*.

Claims 1, 5-8 and 11-18 are drawn to a method of inhibiting the biological activity of transforming growth factor β on predamaged neurons in cerebral disorders, said

method comprising the steps of providing a patient having predamaged neurons and treating said predamaged neurons in said patient with a compound that inhibits the biological activity of transforming growth factor β on said predamaged neurons and a pharmaceutical composition comprising a first compound capable of substantially inhibiting the biological activity of TGF-β on predamaged neurons caused by cerebral disorders and a second compound for disintegrating blood clots wherein the first and second compound are formulated in a pharmaceutically acceptable carrier.

Logan et al, 1991 teach a method of inhibiting biological activity (scar formation) on mammals that had central nervous system injuries (i.e. not intentionally induced) by infusing the mammals with TGF-β blocking antibodies. Logan et al, 1991 teach that these mammals showed reduced fibrotic scar of limited depth (see the Abstract). Logan et al, 1991 also teach a pharmaceutical composition comprising an TGF-β antagonist (e.g. TGF-β blocking antibodies) (see the Abstract).

Logan et al, 1991 do not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Logan et al *(Brain Research, 1992)* teach that if the formation of glial /mesodermal scar is dependent on the well-described ability of TGF-β to stimulate astroglia and matrix deposition then there is therapeutic value of developing TGF-β

antagonists to block matrix deposition and enhance the functional recovery from CNS injury and trauma (page 224).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Logan et al, 1991 used in the method for inhibiting the biological activity of TGF on predamaged neurons in cerebral disorders because Logan et al *(Brain Research, 1992)* suggests that there is a potential therapeutic use of TGFβ antagonists in the CNS to help limit the pathogenesis associated with matrix deposition in the wound (see the Abstract). Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al to the pharmaceutical composition as taught by Logan et al , 1991 because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator to a composition comprising TGFβ antagonists would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

It should be noted that Applicant has not provided support for the newly recited claim limitation "not intentionally induced". The following art rejections are maintained since Applicant has not shown support for the amended claims.

Rejections Maintained

9. The rejection of claims 1, 14-15 and 18 under 35 U.S.C. 102(b) as anticipated by Logan *(WO 93/19783)* is maintained for the reasons set forth on pages 2-4 paragraph 4 of the previous Office Action.

The rejection was on the grounds that Logan *(WO 93/19783)* teaches the use of anti- transforming growth factor β (TGF-β) antibodies, Arg-Gly-Asp containing peptides, decorin and its functional equivalents such as biglycan and TGF-β antagonists to prevent, treat or suppress central nervous system pathology. Logan *(WO 93/19783)* also teaches pharmaceutical compositions containing these agents, which can be administered to patients to inhibit or enhance the production of extracellular matrix in the central nervous system (see the Abstract).

Since the Office does not have the facilities for examining and comparing applicant's compound with the compound of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the compound of the prior art does not possess the same material structural and functional characteristics of the claimed compound). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Logan et al teach providing a subject having surgically induced brain lesions and the newly amended claims recite that the cerebral disorder is not intentionally induced.

Applicant's arguments filed December 3, 2004 have been fully considered but they are not persuasive. Logan *(WO 93/19783)* teaches a method of inhibiting he biological activity of TGF by administering TGF-β antagonists to animals with cerebral

disorders. This rejection is maintained for reasons of record based on the above new matter rejection set forth on pages 3-4, paragraph 4 above.

10. The rejection of claims 1 and 14-18 under 35 U.S.C. 102(b) as anticipated by Melton et al is maintained for the reasons set forth on pages 6-7 paragraph 8 of the previous Office Action.

The rejection was on the grounds that Melton et al teach a method of inducing neuronal differentiation and preventing the death and/or degeneration of neuronal cells *in vitro* and *in vivo* (page 4). Melton et al teach that the antagonizing agents inhibit the activity of TGF-β (page 4). Melton et al teach that the antagonizing agents (i.e. follistain, a protein containing at least one follistain module and a truncated receptor for a growth factor of the TGF-β family) of the invention can bind to growth factor and sequesters the growth factor such that it cannot bind its receptors (page 4). Melton et al teach that the invention can be used to treat neurodegenerative disorders including anoxia-ischemia, Alzheimer's disease, Parkinson's disease, neuronal damage resulting from trauma and neural degeneration (page 5). Melton et al also teach that the invention can be used to treat patients with ALS (page 17). Melton et al teach that the antagonizing agents can be administered by many administration routes such as intravenous and oral administration (page 19).

Since the Office does not have the facilities for examining and comparing applicant's method with the method of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed method and the method of the prior art (i.e., that the method of the prior art does not possess the same material method steps and parameters of the claimed method). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that Melton et al do not teach inhibition of the biological activity of TGF-β as required by the claimed method and pharmaceutical composition. Applicant urges that neural induction is inhibited by activin or interaction with the truncated activin receptor and this teaching distinguishes the claimed invention from the prior art.

Applicant's arguments filed December 3, 2004 have been fully considered but they are not persuasive. Melton et al discloses a method for inducing neuronal differentiation and preventing the death or degeneration of neuronal cells *in vivo* by antagonizing a signalling pathway for a growth factor of the TGF-β family and pharmaceutical preparations comprising a neutralizing agent capable of antagonizing said pathway (Abstract; p. 18, lines 7-11). This method is applied therapeutically and can be used to treat neurodegenerative disorders associated with the progressive loss of neuronal cells such as neuronal damage resulting from anoxia-ischemia or other cerebral disorders (p.5, lines 4-11 ; p. 45-48, claims 1 , 16, 27-40). The method comprises the use of an agent capable of antagonizing the biological action of a protein of the TGF-β, the antagonist acting by competitive or non-competitive binding to a cell-surface receptor for the growth factor, sequestration of the growth factor or inhibition of signal transduction events mediated by the growth factor receptor (p.5, line 33 to p. 6, line 4). Since the method described in Melton et al is explicitly encompasses methods to treat neurodegenerative disorders associated with neuronal damage resulting from anoxia-ischemia and the loss of neuronal cell the prior art reference anticipates the claimed invention.

11. The rejection of claims 1, 5-8, 11-13 and newly presented claims 14-18 under 35 U.S.C. 103(a) as being unpatentable over Logan *(WO 93/19783)* in view of Mattson et al and in further view of Alexander et al is maintained for the reasons set forth on pages 8-10, paragraph 9 of the previous Office Action.

The rejection was on the grounds that Logan *(WO 93/19783)* teaches methods of for preventing, suppressing or treating a central nervous system pathology by contacting tissue with an agent (i.e. anti -TGF-β antibodies and TGF-β antagonists) that inhibits TGF-β activity (see the Abstract). Logan *(WO 93/19783)* teaches that after a penetrating injury of the brain or spinal cord (which include predamaged neurons), there is a failure of axonal growth (page 1). Logan *(WO 93/19783)* teaches that there are no therapies available to promote successful regeneration and functional reconnection of damaged neural pathways (predamaged neurons) (page 2). Logan *(WO 93/19783)* also teach that compositions containing the TGF-β inhibitors can be administered by infusion (i.e. intravenously) (Example 2). However, Logan teaches a method of administering agents including anti -TGF-β antibodies and TGF-β antagonists) to inhibit the activity of TGF-β in the central nervous system (page 3).

Logan *(WO 93/19783)* does not teach the use of compound for disintegrating blood clots.

Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Alexandria et al teach that tissue plasminogen activator is effective in lysing blood clots in animals.

Mattson et al teach that neuroprotective factors such as TGF-β are expressed in response to brain injury (see the Abstract). Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs (page 5).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to add the urokinse or tissue plasminogen activator of Alexandria et al to the pharmaceutical compositions comprising TGF-β antagonists of Logan *(WO 93/19783)* used in the method for inhibiting the biological activity of TGF on predamaged neurons in cerebral disorders because Mattson et al teach that within minutes following traumatic brain injury, metabolic activity is rapidly depressed and edema and hemorrhage occurs. Therefore, one of skill in the art would be motivated to add the urokinase and plasminogen activator as taught by Alexander et al because Alexander et al teach that urokinase and anticoagulants are recommended for treatment when patients are at risk for cerebral hemorrhage. Additionally, Alexander et al has shown that tissue plasminogen activator is effective in lysing blood clots in animals. It would be expected barring evidence to the contrary that the addition of urokinase or tissue plasminogen activator would disintegrate blood clots because it is well known in the art that the prevention of blood clots would be necessary for treatment of central nervous systems disorders to stop cerebral hemorrhaging.

Applicant urges that in order for a case of *prima facie* obviousness to be established, the combination of references must teach or disclose all claim limitations. Applicant urges that Logan does not teach a subject having a cerebral disorder that is not intentionally induced. Applicant urges that the rejection should be withdrawn.

Applicant's arguments filed December 3, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that applicant argues the references individually without clearly addressing the combination of teachings. It is the combination of all of the cited and relied upon references which make up the state of the art with respect to the claimed invention. It should be noted that Applicant makes no mention of the other references (Mattson et al, 1994 and Alexander et al, 1990) used in the 103(a) rejection. To address Applicant's comments regarding establishing a case of *prima facie* obviousness, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 872-9306.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272-0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
April 13, 2005